

Remarks

Amendments to the Claims

Claim 1 has been amended to delete “an antioxidant selected from the group consisting of . . . (ii) an oxygen or free radical scavenger, (iii) a chelating agent, and (iv) mixtures thereof.” Dependent claim 6 has been canceled as redundant. Dependent claim 10 has been amended to recite that the composition of claim 1 further comprises an antioxidant selected from the group consisting of an oxygen or free radical scavenger and a chelating agent and the antioxidant; claim 1 as originally filed supports this amendment.

The amendments add no new matter.

Rejections Under 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 1-32 under 35 U.S.C. § 112, first paragraph, as both insufficiently described and not enabled. Both of these rejections are based on an alleged lack of description of the genus “TFPI variants” as recited in independent claim 1. Claim 6 has been canceled. Applicants respectfully traverse the rejections of claims 1-5 and 7-32.

Written Description

Claims 1-32 are directed to aqueous compositions which comprise TFPI or a TFPI variant. The U.S. Patent and Trademark Office must presume the description of these compositions in the specification as filed is adequate unless there is a reasonable basis to challenge its adequacy. *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). It is, therefore, the Office’s burden to present a preponderance of evidence why a person skilled in the art would not recognize in the present specification a description of the genus of

“TFPI variants.” *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976; M.P.E.P. § 2163.04.

Whether the specification meets the written description requirement for the claimed subject matter is a question of fact. *Vas-Cath v. Mahurkur*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Thus, the M.P.E.P. requires a written description rejection to set forth express findings of fact:

In rejecting a claim, **the examiner must set forth express findings of fact** which support the lack of written description conclusion. These findings should:

(A) Identify the claim limitation at issue; and

(B) Establish a *prima facie* case **by providing reasons why** a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

M.P.E.P. § 2163.04 (“Burden on the Examiner with Regard to the Written Description Requirement), internal reference omitted, emphasis added. The rejection does not set forth express findings of fact to support element (B). Thus, no *prima facie* case of lack of written description has been made.

The specification can provide an adequate written description of the genus of TFPI variants by sufficiently describing a representative number of species within the genus. Written Description Guidelines, 66 Fed. Reg. 1099, 1106 (January 5, 2001). The U.S. Patent and Trademark Office’s Written Description Guidelines define “a representative number of species” and list options for describing a genus by describing a representative number of species:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics,

i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics

A “representative number of species” means that the species which are adequately described are representative of the entire genus. . . . What constitutes a representative number is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

66 Fed. Reg. 1099, 1106 (January 5, 2001) (internal references omitted)

The present specification explicitly describes numerous representative species of TFPI variants which fall within the recited genus. See paragraphs 26-29:

[26] TFPI variants include analogs and derivatives of TFPI, as well as fragments of TFPI, TFPI analogs, and TFPI derivatives. TFPI variants can be obtained from human or other mammalian sources, synthesized, or obtained by recombinant techniques. Analogs are TFPI molecules with one or more amino acid substitutions, insertions, deletions, and/or additions. Conservative substitutions, in which an amino acid is exchanged for another having similar properties, are preferred. Examples of conservative substitutions include, but are not limited to, Gly↔Ala, Val↔Ile↔Leu, Asp↔Glu, Lys↔Arg, Asn↔Gln, and Phe↔Trp↔Tyr. They typically fall in the range of about 1 to 5 amino acids (*e.g.*, 1, 2, 3, 4, or 5 amino acids). Additional amino acids can be added at any position in the molecule, particularly at the amino- or carboxy terminus. For example, one TFPI analog, N-L-alanyl-TFPI (“ala-TFPI”), has an additional alanine residue at the amino terminal end. Amino acid additions may be 1, 2, 5, 10, 25, 100, or more additional amino acids. Fusion proteins are encompassed within the definition.

- [27] Fragments are portions of TFPI, TFPI analogs, or TFPI derivatives. Examples of fragments include Kunitz domains 1, 2, or 3, Kunitz domains 1 and 2 or 2 and 3, or deletions of the N-terminus, C-terminus or both. Substantial guidance for making variants is found in U.S. 5,106,833. Fragments of TFPI comprise at least 20 consecutive amino acids of SEQ ID NO:1. For example, a fragment can be 20, 25, 30, 50, 100, 150, 200, 250, or 275 consecutive amino acids in length. TFPI fragments not possessing biological activity are described in U.S. 5,106,833. Use of such fragments in the present invention is also contemplated.
- [28] Derivatives are defined as TFPI, TFPI analogs, or TFPI fragments having additional moieties. Examples of such additions include glycosylation, phosphorylation, acetylation, or amidation.
- [29] Percent homology between a TFPI variant and SEQ ID NO:1 is determined using the Blast2 alignment program (Blosun62, Expect 10, standard genetic codes, open gap 11, extension gap 1, gap x_dropoff 50, and low complexity filter off). TFPI variants will generally have about 70% or greater, preferably about 80% or greater, more preferably about 90% to 95% (*e.g.*, 90, 91, 92, 93, 94, or 95%) or greater, and most preferably about 98% or 99% amino acid sequence identity to SEQ ID NO:1.

The Office Action provides no findings of fact or reasons to support the assertion that one skilled in the art at the priority date of this application would not have recognized in the specification a description of TFPI variants. The Office Action cites no basis for concluding that this specification does not provide a representative number of species within the recited genera of TFPI variants. Even in an “unpredictable art” applicants “are *not* required to disclose *every* species encompassed by their claims” *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218, (C.C.P.A. 1976) (emphasis in original). Otherwise, a specification would have to

describe explicitly every species within a claimed genus; that is not the law. *See Engel Indus., Inc. v. Lockformer Co.*, 946 F.2d 1528, 1531, 20 U.S.P.Q.2d 1300, 1302 (Fed. Cir. 1991).

The Office Action cites *Fiers v. Revel*, *Amgen v. Chugai*, and *Fiddes v. Baird* for the proposition that the specification does not describe TFPI variants because conception of TFPI variants “cannot be achieved until reduction to practice has occurred.” Office Action at page 6, third full paragraph. Reliance on this case law is misplaced. These cases address what is required for a written description or conception of new genetic material. Applicants do not claim new genetic material. Applicants claim an aqueous composition which comprises either TFPI or a TFPI variant. *Fiers*, *Amgen*, and *Fiddes* are not relevant to the pending claims.

The Office Action provides no scientific reasons or legal precedent why, in view of the specification as filed, a person skilled in the art at the application’s priority date would not have recognized that the inventors possessed the invention of claims 1-32. The specification’s description of “TFPI variants” is sufficient under controlling Federal Circuit precedent to meet the written description requirement of 35 U.S.C. § 112, first paragraph. Applicants respectfully request withdrawal of the rejection.

Enablement

To reject claims 1-5 and 7-32 as not enabled, the Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). The Office must not only explain why it doubts the statements in the specification’s supporting disclosure, but also must support its assertions “with acceptable evidence or reasoning which is inconsistent with the contested statement.” *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370. In this case, the U.S. Patent and Trademark Office has not met its burden.

Claim 1 as amended is directed to an aqueous composition comprising (1) about 0.05 to about 15 mg/ml of TFPI or TFPI variant; (2) about 50 to about 600 mM of a solubilizing agent selected from the group consisting of (i) arginine or an analog thereof, (ii) lysine or an analog thereof, and (iii) mixtures of (i) and (ii); and (3) an oxygen displacement gas. Claim 1 also recites particular characteristics of the composition: a percent aggregation stability of about 45% or greater; a percent oxidation stability of about 45% or greater; and a pH from about 4 to about 8. The Office Action discusses several of the *Wands* factors in an effort to demonstrate that the specification does not enable this subject matter. Rather than support the rejection, however, consideration of these factors actually favours a finding of enablement.

Breadth of the claims and nature of the invention

The Office Action contends that “TFPI variant” is not adequately described; thus, the claims are too broad. As explained above, however, the specification explicitly describes numerous representative species of TFPI variants which fall within the recited genus. See paragraphs 26-29.

Working examples, state of the art, and relative skill in the art

The Office Action faults the specification for providing working examples only for the TFPI variant ala-TFPI. This does not support non-enablement. First, working examples are not required. *In re Long*, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). Second, the specification is addressed to those of skill in the art, and the relative skill of those in the relevant art must also be considered. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. Interf. 1986). As the Office Action acknowledges, the skill of those in the art is high.

Predictability of the art

The Office Action asserts that what is encompassed by “TFPI variant” is not predictable because “those variants are not disclosed in the specification.” Office Action at page 5, line 1. The specification describes and defines TFPI variants; those skilled in the art can readily determine whether any particular polypeptide falls within the scope of “TFPI variant.”

Guidance provided in the specification and quantity of experimentation required

The specification provides substantial guidance for how to make and use the claimed aqueous compositions. The specification provides descriptions of TFPI and TFPI variants (paragraphs 25-29). The specification teaches how to make TFPI and TFPI variants (paragraphs 30-34) and preferred concentrations of these polypeptides in the claimed compositions (paragraph 35). The specification discloses amino acid solubilizing agents and their preferred concentrations (paragraphs 36-39). The specification also discloses the recited antioxidants and how to use them in making the claimed aqueous compositions (paragraphs 40-52). Suitable buffers are disclosed in paragraphs 53-59. Methods of preparing the compositions are taught in paragraphs 62-64. The specification teaches that administration of compositions comprising TFPI or TFPI variants was well known in the art when this application was filed (paragraph 04).

In view of the guidance provided in the specification, the high level of skill in the art, and the state of the art at the time of the invention, it would not have required undue experimentation for the skilled worker to make and use the claimed aqueous compositions.

The Office Action does not make a *prima facie* case that claims 1-32 are not enabled. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 1-3 and 7-9 Under 35 U.S.C. § 112, second paragraph

The Office Action contains four rejections under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse each of these rejections.

The Office Action contends that claim 1 is indefinite because the full name of “TFPI” is not spelled out. Claim 1 has been amended to substitute “Tissue Factor Pathway Inhibitor (TFPI)” in place of the first instance of “TFPI.”

The Office Action also asserts that the recitations “TFPI variant” (claims 1, 2, 3, and 7), “about 70% or more homologous to TFPI (SEQ ID NO:1)” (claim 2), and “enriched” (claims 8 and 9) are indefinite. Under the second paragraph of 35 U.S.C. § 112, the relevant inquiry

... is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed -- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

In re Moore, 439 F.2d 1232, 1235, 58 C.C.P.A. 1042, 1046-47 (1971) (internal reference omitted). Each of claims 1, 2, 3, 7, 8, and 9 is definite under this standard.

Paragraphs 26-29 describe and define the term “TFPI variant” as recited in claims 1, 2, 3, and 7. See the discussion in connection with the written description requirement, above.

Claims 8 and 9 recite “nitrogen enriched air” and “nitrogen enriched oxygen.” Paragraph 43 of the specification explicitly defines what the claim terms “nitrogen enriched air” and “nitrogen enriched oxygen” mean: “‘Nitrogen enriched air’ and ‘nitrogen enriched oxygen’ are mixtures of nitrogen and air or oxygen, respectively, having a nitrogen concentration greater than that found in the atmosphere (*i.e.*, greater than about 79 vol-%).”

The specification defines the percent homology of TFPI variants to TFPI in paragraph 29:

- [29] Percent homology between a TFPI variant and SEQ ID NO:1 is determined using the Blast2 alignment program (Blosun62, Expect 10, standard genetic codes, open gap 11, extension gap 1, gap x_dropoff 50, and low complexity filter off). TFPI variants will generally have about 70% or greater, preferably about 80% or greater, more preferably about 90% to 95% (e.g., 90, 91, 92, 93, 94, or 95%) or greater, and most preferably about 98% or 99% amino acid sequence identity to SEQ ID NO:1.

These teachings of the specification cannot be ignored; in fact, "no claim may be read apart from and independent of the supporting disclosure on which it is based." *In re Cohn*, 438 F.2d 989, 993, 58 C.C.P.A. 996, 1001 (C.C.P.A. 1971).

Claims 1, 2, 3, 7, 8, and 9 are definite. Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 103(a)

The Office Action contains four rejections under 35 U.S.C. § 103(a):

- claims 1-32 stand rejected as obvious over Petersen *et al.*, US 2003/0092627 (“Petersen”);
- claims 1-32 stand rejected as obvious over Chen, U.S. Patent 6,525,102 (“Chen”) in view of Kosoglou *et al.*, US 2002/0147184 (“Kosoglou”);
- claims 14 and 15 stand rejected as obvious over Chen in view of Kosoglou and Takturi, U.S. Patent 5,272,135 (“Takturi”); and
- claims 6-9 stand rejected as obvious over Chen.

Claim 6 has been canceled. Applicants respectfully traverse the rejections of claims 1-5 and 7-32 and request withdrawal of these rejections.

Independent claim 1 is directed to aqueous compositions comprising three components: (1) about 0.05 to about 15 mg/ml of TFPI or TFPI variant; (2) about 50 to about 600 mM of a solubilizing agent; and (3) an oxygen displacement gas. The solubilizing agent is either (i) arginine or an analog of arginine; (ii) lysine or an analog of lysine; or (iii) mixtures of (i) and (ii). The aqueous composition of claim 1 has a pH from about 4 to about 8 and particular stability properties. Such compositions have a percent aggregation stability of about 45% or greater and a percent oxidation stability of at about 45% or greater.

Obviousness under 35 U.S.C. § 103(a) is a question of law based on several factual inquiries:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). Upon making these factual inquiries, the United States Patent and Trademark Office bears the initial burden of providing sufficient facts to establish a *prima facie* case of obviousness. A *prima facie* case requires three showings:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be some reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P., 8th ed., § 2142. The Office Action does not make a *prima facie* case of obviousness for any of the four rejections.

1. The Rejection of Claims 1-32 Over Petersen

The Office Action cites Petersen as teaching “a pharmaceutical composition (when is single-preparation form) consisting essentially of factor VIIa and factor XIII, and/or **stabilizer**, and/or a detergent, and/or a neutral salt, and/or an **antioxidant**, and/or a preservative, and/or a protease inhibitor, and/or **TFPI inhibitor**.” Office Action at page 9, second full paragraph. The Office Action contends that “the idea of combining TFPI, a stabilizer and an antioxidant was clearly disclosed in Petersen et al.” *Id.*, third full paragraph.

On the contrary, Petersen does not teach or suggest any type of composition comprising TFPI or a TFPI variant. Rather, Petersen discloses pharmaceutical compositions comprising factor VIIa and factor XIII and, optionally a TFPI inhibitor. “TFPI inhibitor” and “TFPI” are two different molecules. Petersen discloses nothing about TFPI or pharmaceutical compositions of any kind comprising TFPI. In fact, Petersen mentions TFPI only to define the term “TFPI inhibitor”:

The term "TFPI inhibitor" means compounds inhibiting the anti-coagulative activity of TFPI (tissue factor pathway inhibitor). The term includes compounds such as those disclosed in European Patent No. 558 529, WO 96/28153 and U.S. Pat. No. 5,622,988. "TFPI" and "EPI" (extrinsic pathway inhibitor) may be used interchangeably.

Peterson does not teach or suggest all the limitations of claims 1-5 and 7-32 and does not render these claims obvious.

2. The Rejection of Claims 1-32 Over Chen and Kosoglou

The Office Action cites Chen as teaching a stabilized liquid pharmaceutical composition comprising TFPI or a TFPI variant, arginine as a stabilizing agent, and succinic acid as a buffering agent (Office Action at page 10, paragraph 3). The Office Action cites Kosoglou as teaching compositions comprising TFPI and at least one antioxidant. Office Action at page 10, last paragraph. The Office Action asserts it would have been obvious to combine the teachings of Chen and Kosoglou because of the need to stabilize TFPI to retain its biological activity. Office Action at page 11, first full paragraph.

Claim 1 as amended is directed to an aqueous compositions comprising TFPI or a TFPI variant, a solubilizing agent, and an oxygen displacement gas. Neither Chen nor Kosoglou teaches or suggests a composition comprising TFPI or a TFPI variant and an oxygen displacement gas.

Chen teaches removal of oxygen by nitrogen purging and degassing but only in compositions comprising IL-2 (Example 2). Chen contains no teaching at all that this method of oxygen removal would be useful in a composition comprising TFPI or a TFPI variant. In fact, Chen teaches that "[t]he major degradation pathway for TFPI was previously determined to be protein aggregation/precipitation." Col. 37, lines 24-25.

Kosoglou does not disclose oxygen displacement gases at all. Kosoglou teaches compositions comprising “at least one sterol absorption inhibitor” and “at least one blood modifier.” Abstract. Kosoglou discloses antioxidants as one of a long list of additional “pharmacological or therapeutic agents or drugs” par. 0384 which may be included in the disclosed compositions. These additional “pharmacological or therapeutic agents or drugs” include:

- cholesterol biosynthesis inhibitors (paragraphs 385-387);
- nicotinic acid and its derivatives (paragraphs 389-391);
- “ACAT” inhibitors (paragraphs 392-393);
- “probucol [an antioxidant] or derivatives thereof . . . which can reduce LDL and HDL levels” (paragraphs 394-395, emphasis added);
- LDL receptor activators (paragraphs 396-397);
- fish oil (paragraph 398);
- natural water soluble fibers (paragraph 399);
- plant sterols, plant stanols, and/or fatty acid esters of plant stanols (paragraph 400);
- antioxidants or vitamins (paragraph 401);
- bile acid sequestrants (paragraph 402-405);
- activators for peroxisome proliferator-activated receptors (paragraphs 406-416);
- ileal bile acid transport inhibitors (IBAT) (paragraphs 417-418);
- cholesteryl ester transfer protein inhibitors (paragraph 419-421);
- hormone replacement agents (paragraphs 422-440);
- obesity control medications (paragraphs 0441);

- cardiovascular agents different from those taught in the specification (paragraph 442);
- blood modifiers different from those taught in the specification (paragraph 422); and
- antidiabetic medications (paragraph 443).

Kosoglou also mentions antioxidants generically in a boilerplate list of additives which can be included in the disclosed compositions. See paragraph 448: “Non-limiting examples of suitable pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders such as starch, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.”

Kosoglou discloses nothing about the stability of any of the disclosed compositions. Kosoglou does not teach that any type of antioxidant, much less an oxygen displacement gas, can be used to stabilize TFPI.

The teachings of Chen and Kosoglou, even if *arguendo* combined, do not teach or suggest all the elements of claims 1-5 and 7-32 and do not render these claims obvious.

3. The Rejection of Claims 14 and 15 Over Chen, Kosoglou, and Takruri

The Office Action adds Takruri to the combination of Chen and Kosoglou to reject claims 14 and 15. Claims 14 and 15 ultimately depend from claim 10. Claim 10 as amended recites that the composition of claim 1 further comprises an oxygen or free radical scavenger or a chelating agent. Dependent claim 14 recites that the oxygen or free radical scavenger is L-methionine. Dependent claim 15 recites that oxygen or free radical scavenger is methionine and that the molar ratio of non-TFPI methionine to TFPI methionine is about 1:1 to about 1000:1.


As discussed above, none of the claims – including amended claim 10 – are obvious over the combination of Chen and Kosoglou. Takruri is cited as teaching the use of methionine to inhibit rapid oxidation of methionine residues and thereby stabilize methionine-containing polypeptides. Office Action at page 12, first paragraph. But Takruri does not teach an oxygen displacement gas as recited in amended claim 1. Takruri therefore does not remedy the deficiencies of Chen and Kosoglou and does not render claims 14 and 15 obvious.

4. The Rejection of Claims 6-9 Over Chen

Claim 6 has been canceled. Claims 7-9 are directed to various aspects of the oxygen displacement gas recited in amended claim 1. As discussed above, Chen does not teach or suggest a composition comprising TFPI or a TFPI variant and an oxygen displacement gas. Chen therefore does not render claims 7-9 obvious.

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